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REVIEW

Studying and modifying brain function with non-invasive brain stimulation

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Abstract

In the past three decades, our understanding of brain-behavior relationships has been significantly shaped by research using non-invasive brain stimulation (NIBS) techniques. These methods allow non-invasive and safe modulation of neural processes in the healthy brain, enabling researchers to directly study how experimentally altered neural activity causally affects behavior. This unique property of NIBS methods has, on the one hand, led to groundbreaking findings on the brain basis of various aspects of behavior and has raised interest in possible clinical and practical applications of these methods. On the other hand, it has also triggered increasingly critical debates about the properties and possible limitations of these methods. In this review, we discuss these issues, clarify the challenges associated with the use of currently available NIBS techniques for basic research and practical applications, and provide recommendations for studies using NIBS techniques to establish brain-behavior relationships.

MAIN TEXT

Some of the main goals of neuroscience are to understand how the brain controls cognition, emotion, and behavior. With the advent of neuroimaging technologies in the last century, it became possible to study the structural and functional brain correlates of behavior and underlying cognitive functions. Establishing these correlations, at various levels of description (cells, circuits, and system), continues to teach us a lot about brain-behavior relationships. However, there is increasing awareness that correlative links alone cannot establish that a measured brain process is indeed necessary or sufficient for a behavior or mental process to occur. This limitation may be particularly relevant in applied settings, where the possible diagnostic and therapeutic usefulness of a neural measure depends on whether it reflects mechanisms that are causally involved in pathological disruption and treatment-induced improvements of behavior. Progress on these questions therefore requires methods that allow researchers to directly assess how experimentally-induced changes in neural processes affect behavior and the underlying mental operations.

In animal models, such assessments are usually performed with invasive methods such as pharmacological interventions¹, reversible cooling deactivation², targeted microstimulation³, and more recently optogenetics⁴. These approaches can provide detailed demonstrations of brain-function relations with high degrees of spatial precision, encompassing even cell-type-specific effects. Unfortunately, many of these methods cannot be applied in a routine fashion in healthy humans. Most human studies on the causality of brain-behavior relationships therefore employ purely non-invasive brain stimulation techniques. These methods originated over 30 years ago, when Merton and Morton demonstrated that running brief electrical currents through the human scalp can

activate the underlying cortex and thereby affect behaviors corresponding to the activated brain areas⁵. This demonstration was a breakthrough, as it established that human brain function can be electrically influenced without opening the skull. The protocol did not catch on widely as it was painful to the participants (currents with intensities of ~20 A were applied through the scalp⁵), but it paved the way for the development of more comfortable methods of transcranial brain stimulation. Since then, two such methods have emerged as mainstays of NIBS in both basic and clinical contexts: *transcranial magnetic stimulation* (TMS), which is based on principles of electromagnetism, and *transcranial electrical stimulation* (tES), which harnesses weak, painless electrical currents applied on the scalp (current intensities of ~1-2 mA).

The number of publications utilizing these methods (and variations thereof) is currently growing exponentially (Figure 1b), perhaps reflecting the field's recognition that solid knowledge on brain-behavior relations needs converging evidence from neuroimaging and causal demonstrations. However, the growing popularity of these methods is accompanied by increasingly critical debates about their putative physiological mechanisms-of-action, proper application, and potential for clinical or applied use. These debates are important, since they indicate that NIBS methods may have come of age enough to warrant more detailed investigations of their potential and possible limitations. At the same time, some of these debates may reflect a lack of widely accepted standards for guiding, evaluating, and interpreting methodical aspects of NIBS studies on brain-behavior relations (guidelines mainly exist for the physiologically safe application of these methods^{6,7}).

In this review article, we outline the possibilities and limitations of NIBS methods for investigations of brain-behavior relationships. We start with a concise overview of the spatio-temporal properties of NIBS effects and the implications of these properties for the use of these methods. In the second part, we will summarize and discuss recent debates about the use of NIBS methods and provide recommendations for how these debates may be addressed productively. Finally, we provide guidelines that may help to increase both the conclusiveness of NIBS studies on brain-behavior relations and the potential usefulness of NIBS protocols for possible translational applications.

Establishing brain-behavior relations with NIBS

While the evidence provided by brain imaging methods is purely correlative, it is invaluable for identifying neural processes that may be targeted with causal manipulation methods. In general, methods to causally manipulate neural activity can operate at different levels of spatial specificity (micro-, meso-, and large-scale) and temporal resolution (from milliseconds to days or even longer). In both these dimensions, NIBS methods generally cover the middle ground, but specific ways of applying these methods differ in their precise properties (Figure 1a). In terms of spatial resolution, the two most popular methods (TMS and tES) lead to electric fields that span relatively large areas of tissue compared to the effects of other, invasive methods (Figure 1a and Box 1). Therefore, claims about the spatial focality of the effects need to be interpreted with care and should, whenever possible, be validated with combinations of neuroimaging methods and computational modelling (we discuss this in more detail in the recommendations section, below). Despite the relatively wide spatial spread of the electric fields across

large numbers of neurons, the “effective” spatial resolution for modulating various types of behaviors is thought to be somewhat higher (Box 1 and Box Figure 1). This may reflect that the behaviorally critical neural processes affected by the stimulation can themselves be restricted to a relatively small number of cell groups within larger brain regions, and that the stimulation can have different effects on neurons that are at rest or activated by ongoing behavior^{8,9}. The functionally-relevant spatial resolution of NIBS methods may therefore differ across different task contexts and may depend on the spatial extent of the task-related ongoing neural processing. Moreover, different ways of applying the same NIBS method can differ in their precise physical properties, which can set different limits on their mechanism-of-action, physiological effects, and spatial/temporal specificity. Different ways of applying NIBS methods are therefore suited to test different types of hypotheses regarding physiology-behavior/cognition interactions.

For instance, online application of TMS (i.e., single- or double-pulse TMS, or short bursts of TMS¹⁰) elicits temporally restricted bursts of action potentials. The application of such TMS pulses during task performance can be used to selectively interfere with ongoing neuronal processes to study the temporal dynamics of brain function with high temporal resolution (in the order of milliseconds). For examples, TMS pulses applied over V1 at a specific latency from the onset of a visual stimulus can induce suppression of conscious visual perception of this stimulus¹¹ and TMS pulses applied over cortical language production areas can produce speech arrest within a specific timeframe¹². Additionally, simultaneous application of TMS pulses over different interconnected brain areas¹³ or during concurrent neuroimaging^{14,15} (Figure 2c) allows tests of how action potentials elicited in one brain area impact on processing in interconnected areas in a

top-down and/or context-sensitive manner; this allows direct study of how brain networks dynamically operate at high temporal resolution and may make it possible to stimulate deep cortical or subcortical areas indirectly via interconnected areas^{14,15}. Moreover, online TMS protocols that apply pulses at specific frequencies may facilitate corresponding oscillations, thus allowing tests of the causal link between brain rhythms and behavior^{16–18}. Taken together, these studies demonstrate that online TMS protocols exert influences on neural processing in a highly task-, context-, and time-dependent manner; these protocols can therefore be tailored to affect specific aspects of neural activity.

Other applications of TMS have focused on *neuromodulatory* after-effects following repetitive TMS protocols¹⁰ (rTMS). Depending on their specific frequency and/or patterning, different rTMS protocols result in excitatory or inhibitory after-effects lasting several minutes, which have been linked to long-term potentiation or long-term depression (LTP/LTD, see Box 2), respectively. These after-effects are thought to reflect rTMS influences on the strength of glutamatergic synapses via NMDA receptor, AMPA receptor, and calcium channel effects^{10,19–21}. Other possible mediators of these effects may reflect non-linear time-dependent influences on inhibitory GABAergic neurons, non-synaptic mechanisms including alterations of the brain-derived neurotrophic factor (BDNF, see Box 2), and even neurogenesis²². Given these modulatory impacts of rTMS protocols on brain physiology, their effects by definition critically depend on brain state during the stimulation²³. The duration of the physiological aftereffects makes these “offline” rTMS protocols well-suited to study the causal contributions of cortical regions to behavior in both health^{24–26} and disease^{27–29}. Studies employing this approach measure

behavioral alterations in the immediate aftermath of the rTMS protocol, thereby testing the functional consequences of the temporary excitability modulation for behavior.

The second family of methods – tES – produces its neuromodulatory effects not via magnetic fields (as TMS does) but rather by means of weak electrical currents applied on the scalp. The most popular variant is transcranial direct current stimulation (tDCS), introduced about two decades ago (Figure 1b). This method applies a weak tonic direct current between electrodes mounted on the head, which partially passes through the cortical tissue and affects relatively large cortical areas (on the order of centimeters, see Box 1). This current de- or hyperpolarizes neuronal resting membrane potentials and thereby alters cortical excitability^{30,31}. The primary effects of tDCS do not include synaptic mechanisms but instead involve voltage-dependent ion channels³². However, stimulation extending over a few minutes leads to LTP- or LTD-like plasticity^{32,33} that can extend to inter-connected cortical and subcortical structures^{34,35}. The temporal resolution of this technique is low, as the online neuromodulatory effects start to take place few seconds after the begin of the stimulation and continue throughout current application, whereas the physiological aftereffects can last for several hours and even days if accompanied by pharmacological interventions³². Thus, considering the physiology and neuromodulatory characteristics of tDCS, the functional specificity of the intervention largely relates to its capability to modulate task-related neural processing rather than to the spatial and temporal specificity of the electric fields produced by the stimulation itself³⁶.

While tDCS has low temporal resolution and is indiscriminate as to which aspects of neural processing are modulated, other variants of tES methodology can be used to target more specific aspects of neural function at higher temporal scales. One such

method was specifically developed to investigate the role of neural oscillations in designated frequency bands for behavior³⁷. This technique – known as transcranial alternating current stimulation (tACS) – employs oscillatory electrical stimulation with the aim of facilitating neuronal activity in specific frequency bands^{38–40}, thereby allowing study of causal links between brain rhythms and specific aspects of behavior^{41–44}. For instance, tACS can be used to study the causal role of theta-gamma cross-frequency coupling for working memory performance⁴⁵, the contributions of beta and gamma oscillations to motor behavior^{41,43}, the role of frontal gamma oscillations during high level cognitive tasks⁴⁶, or the causal contributions of alpha oscillations to the generation of visual and crossmodal perceptual illusions^{42,44}.

tACS can also be used to investigate how oscillatory coherence between spatially distinct nodes of functional networks contributes to behavior^{47–50}, by simultaneously applying oscillatory currents over distinct regions at the same frequency, but using different oscillatory phases to facilitate or hamper synchronization in the functional networks (Figure 2a). As mentioned before, the link between rhythmic oscillations and behavior can also be investigated using rTMS protocols that apply pulses at specific frequencies to facilitate corresponding oscillations^{16–18}. Crucially, emerging work starts to suggest that TMS pulses may have very different effects if they are applied at different phases of ongoing neural oscillations⁵¹. This shows directly that some of the variability of neural NIBS effects may relate to the precise temporal relation between the NIBS protocol and ongoing neural activity, suggesting that this information could be used to design more efficient stimulation protocols in the context of closed-loop systems^{52–54}.

A limitation of the frequency-specific protocols mentioned above (and tES methods in general) is that they can only directly affect activity in cortical regions. Direct stimulation of deeper structures typically requires invasive procedures, for example deep brain stimulation (DBS). However, there are attempts to develop specific TMS hardware – e.g. the TMS H-coil⁵⁵ – to modulate the excitability of brain areas lying further away from the cortical surface (possibly up to 6 cm)⁵⁶. Moreover, a recent study showed in mice that a new NIBS protocol, termed temporal interference (TI), allows entrainment of oscillatory neuronal activity in subcortical structures (such as the hippocampus) without recruiting neurons of the overlying cortex⁵⁷. Future extension of this TI-NIBS protocol to humans, if at all possible, may therefore overcome the constraint that only superficial structures may be directly affected.

While numerous studies have demonstrated selective and frequency-specific effects of tACS on behavior, it is debated how exactly these protocols affect oscillatory activity. Work in anesthetized animals and computational modelling suggests that direct neural entrainment is possible^{39,40}, but there is little evidence in humans that this is indeed the case. However, studies are starting to investigate the neural consequences of tACS *in vivo*. For instance, 10-Hz tACS applied over the motion sensitive area (MT) attenuates visual motion adaptation in humans⁸ and reduces spike-frequency adaptation of MT neurons in macaques⁹. These findings provide a direct demonstration that weak alternating electric fields applied to the scalp, which change motion adaptation behaviorally, in fact significantly affect neural processing in a frequency-specific manner. However, this study could not directly demonstrate neural entrainment due to technical complications with recording during externally applied electrical fields^{58,59}. Thus, the

investigation of how tACS entrains or modulates oscillatory activity in the human brain will require the development of multi-modal NIBS-recording techniques and well-validated artifact rejection methods capable of identifying neural oscillations during stimulation^{58,59}.

Another related tES technique called transcranial random noise stimulation (tRNS) focuses on the link between behavior and frequency-specific noise inherent in neural processing⁶⁰. Compared to other stimulation methods, relatively little is known about the physiological impact of this method. However, only 10 minutes of tRNS applied over M1 can enhance motor cortex excitability for about 60 minutes after the end of stimulation, suggesting that this method may induce neuroplastic effects⁶⁰ of similar strength as those induced by anodal tDCS. Applied in conjunction with cognitive tasks, tRNS protocols may enhance learning performance even more strongly than anodal tDCS does^{61,62}. Interestingly, the effects of tRNS are strongest when used at intensities thought to induce optimal noise levels⁶³ (Figure 2b), consistent with the stochastic resonance principle (see Box 2). tRNS may thus prove useful for investigating the stochastic dynamics of neuronal processing in the intact human brain⁶⁴.

Standard NIBS studies using the approaches mentioned above typically apply these protocols in purely behavioral settings, targeting brain areas identified by previous neuroimaging research and assuming that the NIBS methods exert uniform and clearly interpretable physiological effects on these areas. This standard approach has been used for studying causal brain–function relationships in numerous domains, including vision⁶⁵, audition⁶⁶, motor^{67–69}, somatosensation⁷⁰, language^{71,72}, attention^{73,74}, memory^{75,76}, reasoning^{46,77}, decision making^{78–80} and social behavior^{81–83}. While this approach continues to yield very interesting demonstrations that specific aspects of behavior can

be changed by stimulation, and therefore causally relate to the affected neural processes, it has also triggered critical debates about the properties and possible limitations of these methods. We will discuss these in the following section.

Current controversies associated with the use of NIBS

Over the past few years, critical discussions have arisen about the replicability of effects reported in various scientific fields^{84,85}. For studies using NIBS, this discussion has focused on both physiological and behavioral effects of these techniques. However, this general discussion often has not explicitly differentiated between *deterministic* and *neuromodulatory* NIBS approaches. The former methods – e.g., single- or double-pulse TMS, or short bursts of TMS¹⁰ – directly elicit action potentials that may have relatively uniform physiological and behavioral effects (even though some intra- and interindividual variability can be observed⁸⁶). The latter – e.g., offline rTMS or tES methods – mainly operate by modulating ongoing brain activity, so that the effects of these methods will by definition depend critically on brain state and task context. This state-dependency of neuromodulatory NIBS effects is confirmed by animal studies showing, for instance, that the ability to induce LTP and LTD is critically shaped by the previous learning experience of the targeted cortical area⁸⁷. Indeed, in humans, the effects of rTMS and tES on cortical excitability (as monitored by TMS-generated MEPs) varies between individuals, as do stimulation effects on other physiological and cognitive-behavioral variables^{88–92}. However, precise estimates of this variability are so far lacking, as the objectives and methodical procedures of NIBS applications differ considerably between studies. This severely complicates the use of meta-analytic procedures to estimate effect sizes associated with NIBS applications: Such procedures can only validly be applied to

logically coherent sets of effects generated with the same well-defined methodical procedures in the same task contexts. Preliminary attempts at quantifying effect sizes associated with NIBS methods *per se*^{93,94} have therefore been inconclusive, as they have mostly pooled many different studies using this research method in very different ways.

The sources of the reported variability of NIBS effects have hardly been explored systematically, but include brain-intrinsic, task-related, and methodological factors. Relevant *brain-intrinsic factors* may include trait and state variables such as sex, age, diurnal variations, genetic polymorphisms, attention, pharmacology, and synaptic history⁹⁵ (Figure 3). For example, NIBS-induced plasticity has been shown to be related to BDNF polymorphisms⁹⁶ and is altered by enhancement or reduction of dopaminergic neuromodulation in a non-linear, dosage- and receptor-dependent manner^{97–99}. Therefore, the individual variability of NIBS effects is not surprising, as NIBS protocols induce plasticity by affecting glutamatergic, calcium-dependent mechanisms that are affected by various neuromodulatory agents. By definition, these effects will therefore vary between different tasks and brain regions (see below). As for *methodological aspects*, variations of NIBS protocols in terms of intensity, duration, electrode position, and coil orientation can alter stimulation effects, even in a non-linear fashion^{100,101} (see also Box 1). Additionally, the physiological effect of NIBS methods can strongly depend on characteristics of the testing situation, as clearly illustrated by the fact that even MEPs elicited from motor cortex following modulatory NIBS protocols can differ in strength depending on what participants were doing at the time of stimulation (e.g., whether they engaged in motor behavior or not¹⁰²). Finally, subject-specific aspects can also play a role, such as differences in arousal or attentional state, ceiling or floor effects with regard

to task performance, or differences in group size, just to name a few¹⁰³. However, it is important to highlight that many of these sources of variability are not unique to NIBS studies and equally apply to many other research approaches attempting to relate physiology and behavior in the biological and social sciences¹⁰⁴ (Figure 3).

The variability of reported NIBS effects need not be disadvantageous, but may instead provide important information about how interventions may be personalized and optimized^{105,106}. Moreover, this natural variability may help to identify factors that affect naturally occurring plasticity, thereby further elucidating the brain physiology underlying cognitive processes. Future meta-analyses of NIBS effects should therefore attempt to systematically identify the factors that determine the variability of NIBS effects; at the very least, these analyses should only pool studies that indeed investigated the same specific brain-behavior relationship with closely comparable NIBS procedures^{93,104}.

The sources of physiological variability discussed above show that one cannot assume that protocols known to result in enhancement or reduction of primary motor cortex excitability – the most frequently-used assay of physiological NIBS effects – will have the same physiological effect when applied to another brain area. Another factor that may affect the variability of NIBS effects relates to possible non-linear interactions with task-related neural processing. For instance, if NIBS methods and task performance have synergistic effects on the same neuronal populations, neurons may be activated too strongly, thereby resulting in antagonistic NIBS effects^{101,107}. Finally, the link between behavioral performance and physiological measures – such as TMS-generated excitability measures or cerebral activation monitored by functional imaging – may in itself not always be straightforward. For instance, improved performance during motor learning

is known to result in activity reductions in motor cortex networks^{108,109}. However, these reductions obviously do not indicate that the functional relevance of this network has decreased; instead, they may reflect that the selectivity of task-relevant networks has increased⁴³. NIBS protocols may therefore affect performance in opposite ways during different stages of learning, as shown e.g. for visuo-motor coordination¹¹⁰.

One crucial, currently unresolved issue is the question whether tES protocols always elicit their strongest effects under the electrodes, since computational models suggest that the peak of the electric field should lie between the electrodes for some montages (Box 1). Such computational models of tES-induced electric fields may ultimately prove crucial for optimizing the efficiency of NIBS protocols^{106,111}, but it will be crucial to validate their computational predictions both physiologically and behaviorally, and to fully account for well-established effects on areas under the electrodes as induced by traditional protocols³⁶ (see a more detailed discussion on this topic in BOX 1).

Another focus of recent debate is the application of NIBS techniques in a *do-it-yourself* manner, mainly for the purpose of neuro-enhancement. Several companies have begun to produce stimulators specifically for this type of application; for technical and financial reasons, such stimulators are more widely available for tDCS than TMS. It is questionable whether the effects of NIBS approaches are sufficiently uniform and understood to be readily applied for neuro-enhancement purposes in everyday life¹¹². Critics believe that it may be too early to employ NIBS methods as routine neuro-enhancement tools, because the physiological effects vary between individuals (see above) and because important translational questions needed for everyday use of NIBS remain unaddressed. Most of the existing NIBS studies were conducted in controlled

laboratory settings, did not specifically aim for maximal and homogeneous effects, did not explore long-term (and possibly performance-reducing) effects, and did not focus on possible late-occurring side effects or side effects that might be caused by intensified use. Obviously, this cautionary statement does not mean that NIBS will never be suitable for neuro-enhancement purposes; future translational approaches of the basic laboratory studies may offer this possibility if they take state- and task-dependent effects into account, possibly as closed-loop systems⁵².

Apart from these methodological issues, NIBS and all other kinds of neuro-enhancement techniques are subject to ethical considerations. These comprise the question how the techniques need to be applied in order to be appropriate and safe, the problem that there is only limited knowledge about the effects of NIBS on the developing brain¹¹³, and the fact that it is difficult to detect NIBS-related “neuro-doping”¹¹⁴ in contexts in which this may be critical (e.g., standardized exams or sports competitions). More generally, there is considerable debate about whether neuro-enhancement techniques compromise the autonomy of users, either neurophysiologically or by societal means, for instance, if people are pressured into their use or if the associated expense widens the gap between economically diverse groups¹¹⁵. The discussion also encompasses the question whether specific communication strategies¹¹⁶ may be necessary to ensure sufficient transparency so that potential users and policy makers can make informed decisions about the use of NIBS methods. Finally, it is debated how these methods should be regulated¹¹⁶ to prevent the widespread use of insufficiently tested interventions while avoiding unnecessary restrictions on the development of promising intervention tools in the scientific domain.

Overcoming NIBS limitations

Some of the problems discussed in the previous section might relate to the variability of methodical procedures employed in NIBS studies. This variability may reflect a lack of clear guidelines on how conclusive NIBS evidence can be, given the details of how the specific NIBS method was employed and how the resulting effects are interpreted. In this section, we propose some tentative guidelines that may help in both assessing the strength of evidence for brain-behavior relations in NIBS studies and for designing and conducting NIBS studies. These guidelines may provide a starting point for overcoming some of the limitations discussed in the previous section. Note that we focus these guidelines on studies of brain-behavior relations; our recommendations may be neither sufficient nor necessary for basic neurophysiology research using NIBS methods.

Overcoming the limitations of NIBS methods will require both specific methodical procedures as well as combinations of NIBS procedures with other research methods. In our eyes, the more these two strategies are adhered to in a given NIBS study, the more conclusive the evidence for a specific brain-behavior relation can be (Figure 4). For instance, most exploratory and least conclusive may be those studies that acquire only behavioral measures in combination with NIBS application over a target site that is defined purely based on scalp measurements (using for instance the 10-20 system). We expect this type of studies to result in the highest level of variability in effect size. On the other hand, most conclusive (and least exploratory) about a brain-behavior relation may be studies that incorporate the following methodical procedures: First, neuro-navigation in order to more precisely locate the NIBS region of interest in each participant, e.g. based on functional neuroimaging evidence or based on clearly defined anatomical criteria. This

is arguably more critical for TMS studies than for studies employing tES with its relatively coarser spatial resolution. However, tES studies may also benefit from this step since this ensures more homogenous positioning of the areas of interest in the induced fields, in particular for emergent tES protocols that offer higher spatial resolutions (see BOX 1 for a discussion on this topic). Second, control tasks or behavioral measures that ascertain that the NIBS effects are indeed specific for the behavior under study. Third, stimulation of control regions/frequencies in order to test the functional specificity of the target area/neural process of interest. Fourth, combination with neuroimaging in order to directly quantify the strength of the NIBS effect on the local neural effect of interest, and to measure how connected brain networks are affected by the application of the stimulation. Fifth, characterization of the NIBS-induced changes with theory-driven models whose mechanistic latent variables can capture changes in both behavioral and brain activity modulations.

The multi-method approach we propose here may be impractical for clinical use and may have poor ecological validity for standard clinical settings. However, we think it may be decisive for basic research in order to provide conclusive evidence for the effectiveness of a given NIBS protocol. This step appears essential to inform subsequent translational and/or applied clinical use of these methods, which would not have to employ the demanding research pipeline described in Figure 4 but could follow the exact protocol established as effective in prior basic studies.

Adopting the type of multi-method strategies mentioned above are labor-intensive and challenging, but this approach is increasingly adopted and therefore feasible^{18,117–119}. One example study¹¹⁸ that utilized many of the methodical procedures suggested in

Figure 4 tested the hypothesis that working memory information is temporarily stored via “activity silent” synaptic mechanisms (Figure 5a). This study used fMRI to localize cortical areas that represent category specific working memory contents, and TMS combined with EEG to characterize the temporal dynamics of the hypothesized memory reactivation. Another study¹⁸ utilizing similar procedures investigated the causal role of theta oscillations (~6 Hz) on the dorsal stream for working memory maintenance (Figure 5b). The authors used MEG to identify for each individual the cortical generators of theta oscillations related to memory maintenance, and then tested the causal role of these temporal-spatial oscillatory signatures supporting working memory maintenance with combinations of rhythmic TMS and EEG that can test for neural entrainment¹²⁰. A third example study¹¹⁷ demonstrated a causal role for the temporoparietal junction (TPJ) in guiding strategic social behavior, by combining computational modeling of behavior, neural activity recordings with fMRI, and transcranial magnetic stimulation (TMS) guided by neuronavigation (Figure 5c). Notably, in all these studies, the documented effects were shown to be specific for a given task context, brain region, or stimulation frequency. Thus, these example studies demonstrate that NIBS studies can deliver conclusive evidence for a specific, mechanistically defined brain behavior relationship (rather than being purely exploratory) if researchers employ a methodical framework similar to the one illustrated in Figure 4.

Combining NIBS methods with other imaging techniques such as magnetic resonance spectroscopy (MRS) can also provide insight into the specific neurophysiological mechanisms of stimulation effects that go beyond those acquired with pharmacological interventions¹²¹ and that can be linked to cognitive processes¹²². For

instance, it has been shown that anodal tDCS over M1 reduces the concentration of GABA, whereas cathodal stimulation results in a significant decrease in the concentration of both glutamate and GABA¹²³. This is consistent with the notion that LTP-like plasticity in the neocortex – thought to be affected by tDCS – critically depends on GABA modulation¹²⁴. Based on these findings, a recent study employed tDCS to test for cortical rebalancing of excitatory and inhibitory influences during associative learning¹¹⁹. The researchers administered anodal tDCS to induce a local reduction in cortical GABA while using fMRI to track the representational overlap between learned associations over time. As hypothesized, the new experiment revealed that cortical memories were re-exposed during anodal tDCS, thereby illustrating how NIBS in combination with different neuroimaging modalities (MRS and fMRI) can be used to reveal a more comprehensive picture of the neurophysiological mechanisms underlying cognitive processes.

Shifting the field from more exploratory behavioral demonstrations to the multi-method approaches illustrated above requires careful planning of all stages of a NIBS study (Figure 6). That is, during the *design stage* of the experiments, the researchers must already clearly define the area that should be stimulated, the cognitive process that should be modulated, and how this NIBS influence on behavior can be measured conclusively. This latter step requires *a-priori* considerations of including a control task/behavioral measure to establish context-specificity and selecting a control brain region to test the spatial selectivity of the intervention effect. Additionally, in order to reduce problems with type I errors and improve reproducibility¹²⁵, NIBS studies (and all other studies) should employ adequate sample sizes¹²⁶. This may be achieved by power analyses¹²⁶ and the consideration that studies of standard behavioral tasks aiming at

threshold significance levels with sample sizes $n < 20$ are likely to be irreproducible¹²⁷. Finally, during the planning stage, investigators usually have a clear hypothesis of the neural process they want to affect with their protocol. NIBS studies are therefore ideal candidates for pre-registration and we encourage the community to adopt this scientific practice.

During the *execution* stage, the researchers should try to maximize the reliability of the NIBS-induced modulations, e.g., by using neuro-navigation techniques to identify in each individual the target regions of interest based on prior functional and/or structural neuroimaging (but see the caveat about clinical studies described above). Moreover, given that the majority of the NIBS methods induce somato-sensory effects (e.g. in TMS auditory effects of the “coil click”¹²⁸, in tDCS the skin sensations due to the current flow over the scalp¹²⁹, and in tACS the perception of phosphenes¹³⁰), it is crucial that the authors take care of blinding the NIBS intervention and to properly control for placebo effects.

Finally, for the *analysis/report* stage, the investigators should have a clear plan for the statistical analyses used to evaluate whether the targeted cognitive process was specifically impacted by the NIBS intervention. This analysis plan should include statistical comparisons with control tasks, brain regions and clearly defined neuro-computational latent variables to identify the specificity of the hypothesized NIBS-induced effect on behavior and neural function. Last but not the least, in order to promote reproducibility in NIBS research, we encourage both researchers and journal editors to provide for every publication involving any type of NIBS intervention a methods reporting checklist. This type of strategy is already used for studies employing fMRI¹³¹, a research

method that has also triggered intense discussions about methodical practices and reproducibility⁸⁵. Fortunately, corresponding methods-reporting NIBS checklists already exist based on recent international consensus studies for TMS¹³² and tES¹³³. Such checklist reports would ensure transparent reporting of methodological details concerning NBS application, data collection, and data analysis, all of which have clear implication for interpretation and future use of these data¹³¹.

Implications for translational applications

Beyond studies employing NIBS methods to reveal causal brain-behavior relations, important applications of NIBS protocols have always attempted to identify and potentially ameliorate pathophysiological mechanisms underlying neurological and psychiatric diseases. The problems discussed above apply in a similar manner to these more clinical and translational applications of NIBS methods. While the use of NIBS for therapeutic applications has been extensively investigated, the corresponding treatment effects have been moderate and variable in most cases; beyond the use of prefrontal rTMS for treatment of major depression, no NIBS protocol has developed into a routinely-used treatment tool so far¹³⁴. This does not necessarily reflect limited therapeutic potential of NIBS interventions. However, it does suggest that research strategies in this field so far may not have been well suited to develop and identify NIBS protocols with optimal efficacy. At least three lines of research may advance the field in this respect. First, it will be important to base any intervention protocol on solid mechanistic knowledge about the causal and specific contribution of brain areas and networks to clinical symptoms. In analogy to basic-science studies on causal brain-behavior relationships, this knowledge

would have to be derived with combinations of brain stimulation, neuroimaging, solid experimental designs, and modeling work (as attempted e.g. in computational psychiatry¹³⁵). Such initial studies in healthy participants should lead to further translational treatment-validation studies that should not only monitor clinical symptoms but also physiological data, to validate the precise neurophysiological mechanisms causally mediating the intervention effects. Second, promising treatment protocols identified with the strategy discussed above should be further optimized by systematic evaluation of the optimal stimulation areas and parameter settings for the stimulation; this should initially be performed in healthy surrogate populations but should importantly be directly validated in the target patient groups (to account for the state-dependency of neuromodulatory NIBS protocols discussed above). This optimization of intervention protocols may not be restricted to the group level, but should include individual optimization of the protocols dependent on brain state, lesions, clinical symptoms, and other factors. Third, the field is currently characterized by a multitude of studies with relatively small sample sizes. While this may be helpful for exploratory and screening purposes, it is not sufficient for establishing the clinical relevance of an intervention and for decisions about its implementation in clinical routine. Thus, larger and preferably multi-center randomized clinical trials should be conducted to establish with adequate statistical power which protocols may have clinically relevant effects, and on whom. All these steps would be important to provide solid evidence for the usefulness of applying these validated protocols in more basic and less research-oriented clinical settings.

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548 **Conclusions**

549 In the last 30 years, NIBS methods have become indispensable tools for elucidating how
550 behavior causally depends on specific aspects of neural activity in the healthy human
551 brain. There is presently no alternative to these techniques for the study of causal brain-
552 behavior relationships in humans, but current controversies highlight that the use of NIBS
553 for research purposes requires responsible scientific practice. This may necessitate a
554 shift in focus from simplistic assumptions about how NIBS methods generally affect the
555 brain towards more physiologically informed multi-method approaches that test specific
556 hypotheses about how NIBS influences on behavior are mediated by modulation of well-
557 defined neural processes. These approaches should explicitly consider various intrinsic,
558 task-related, and methodological factors that can potentially influence the variability of
559 behavioral and physiological outcomes. Moreover, more attention should be devoted to
560 the precise reporting of methods, protocols and results to allow more accurate
561 interpretations and future summary of the data. Of course, these considerations are not
562 only important for NIBS research but also for other fields of experimental sciences. But
563 the current debates highlight that NIBS research in particular may be at a crossroads
564 where the field would strongly benefit from coordinated methodological efforts to optimize
565 the conclusiveness of findings on brain-behavior relations. This step appears vital for
566 successful translational applications of these methods for cognitive enhancement and
567 improved mental health.

Figure Legends

Figure 1. a) The scheme shows the temporal and spatial resolution at which different causal brain interventions work. NIBS methods work at the meso-scale level, and the temporal resolution varies between high and low depending on the specific NIBS protocol. NIBS necessarily involves the relatively indiscriminate activation of large numbers of neurons; the apparent temporal and spatial specificity seen in NIBS studies is thus unlikely to reflect the anatomical and temporal specificity of the stimulation. Instead, it may indicate disruption of behaviorally-relevant operations that are carried out by a relatively small number of cell groups¹⁰⁷ within larger brain regions **b)** This plot shows the exponentially-growing number of citations per year for TMS, tDCS and tACS (source: ncbi.nlm.nih.gov; search dates from the year 1980 to 2016).

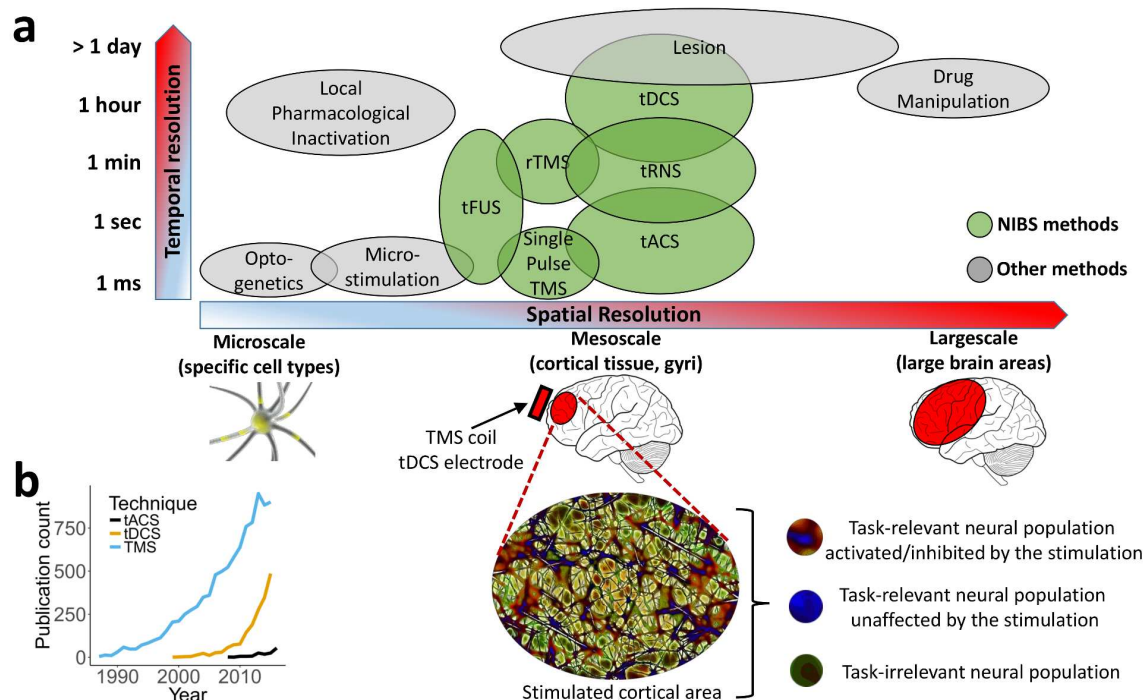


Figure 2. Examples of NIBS methods to study brain-function relationships. **(a)** tACS applied with multi-electrode setups can be used to investigate how oscillatory coherence between spatially distinct nodes of functional networks underlies behavior. In the example experiment presented in this panel, tACS electrodes were mounted over the medial prefrontal cortex (mPFC) and posterior parietal cortex (PPC), two brain regions identified in an EEG experiment to show phase-coupling that was related to the consistency of preference-based decisions¹³⁶. In a subsequent tACS experiment⁴⁸, tACS was applied over the mPFC and PPC at the frequencies identified in the EEG experiment at six different lags ($\Delta\varphi$). This showed that full anti-phase stimulation leads to poorer performance compared to tACS applied at full in-phase stimulation. Crucially, the optimal phase difference for task performance indicated that information may flow from frontal to parietal cortex (see right panel), illustrating that tACS can be used to make inferences about the direction of information flow between segregated nodes of functional brain networks. **(b)** tRNS may be useful for investigating the stochastic dynamics of neuronal processing. In the example presented in this panel⁶³, tRNS was applied over the primary visual cortex (V1, left panel) at different noise amplitudes (middle panel) to investigate the stochastic resonance phenomenon (SR, see BOX 2). Consistent with the assumption that there are optimal noise levels for neural processing, only intermediate (but not high or low) levels of noise led to higher discriminability in a signal detection task (right panel). This illustrates how tRNS can elucidate stochastic dynamics of neural circuits in the intact human brain. **(c)** TMS can be combined with fMRI to reveal functional influences in brain networks underlying behavior. In the example study presented in this panel, the investigators tested different theories about the role of dorsolateral prefrontal cortex

(DLPFC) in stabilizing working memory during external distraction¹⁴. Subjects had to memorize face or house stimuli that activated the fusiform-face area (FFA; for faces) and parahippocampal place area (PPA; for houses) while distractor stimuli from the opposite category were present or not. TMS pulses given to DLPFC during fMRI led to increased BOLD signals in FFA and PPA only when distracters were present. Critically, these influences were only observed in regions representing the current memory targets (right panel), thus providing causal evidence that neural signals from DLPFC can enhance WM representations in posterior brain areas during external distraction.

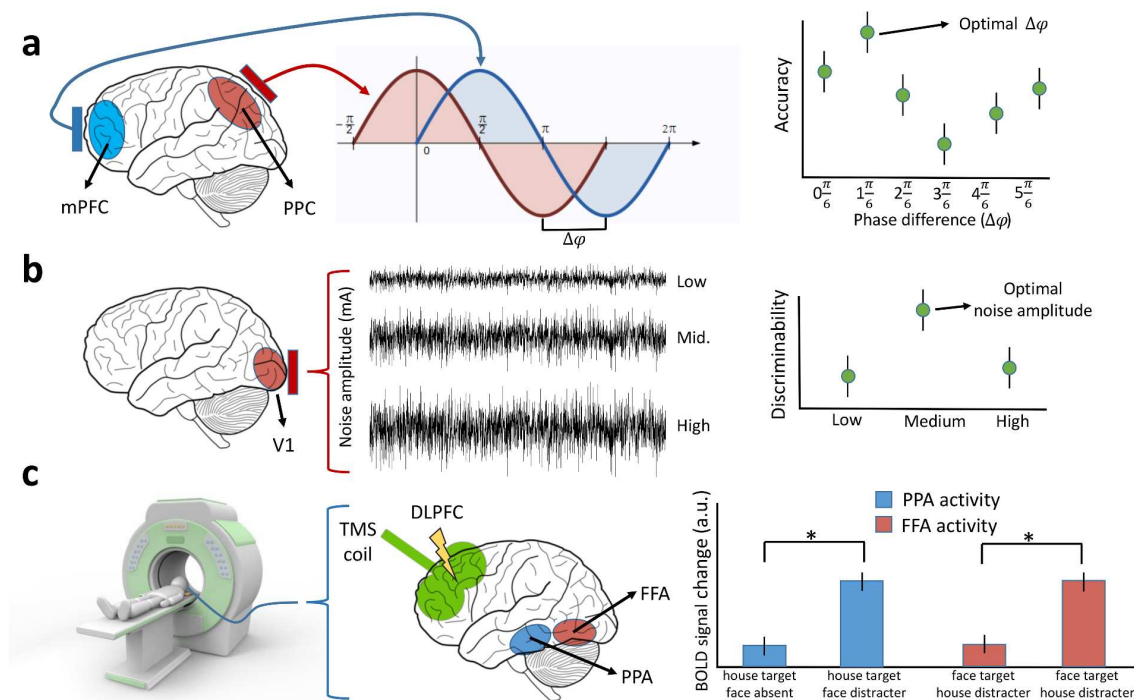


Figure 3. Example factors determining the variability of neurophysiological and behavioral NIBS effects. Many sources of variability in NIBS effects reflect factors that similarly affect the variability of other experimental interventions in the life sciences. However, there are NIBS-specific factors that should be taken into account in both experimental studies and studies employing meta-analytic techniques. The latter also need to ensure that studies are selected for inclusion based on overlap in conceptual aims and well-defined methodical criteria^{93,104}.

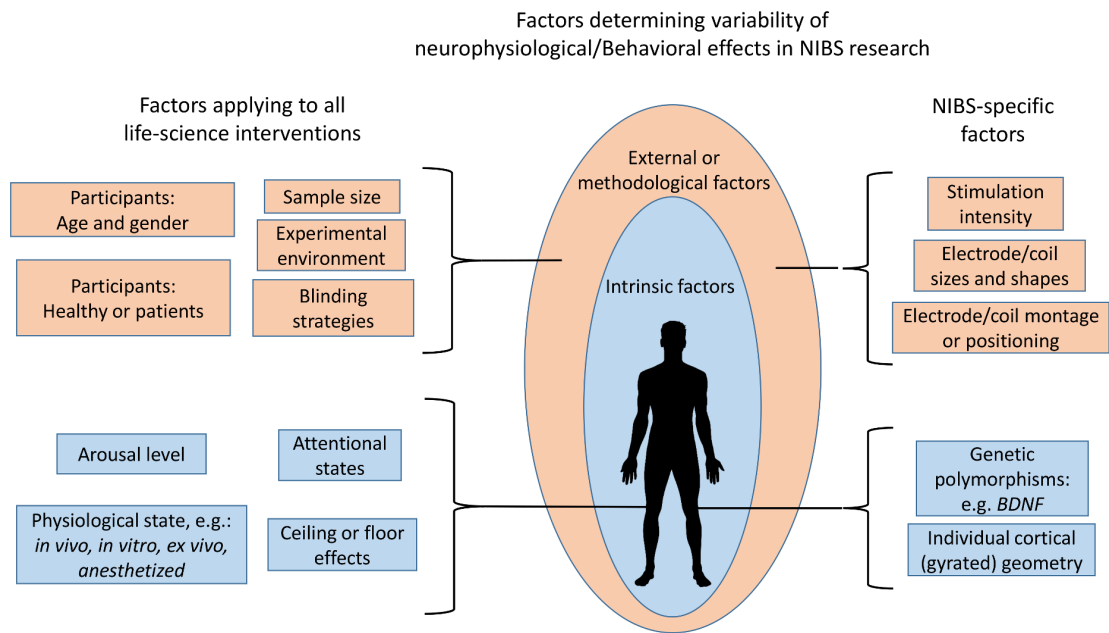


Figure 4. The conclusiveness of NIBS results on brain-behavior relations depends on the degree of methodological effort. Here we show an example decision tree to illustrate how the successive inclusion of methodical procedures in a given study can lead to increasingly conclusive and mechanistically-informed evidence for the relationship

between behavior and a well-defined neural process (for examples, such a scheme was followed in REFs. 18, 117 and 118; see also Figure 5). It is important to note that the scheme is illustrative rather than fully prescriptive, as the precise order of these procedures is not necessarily the same for all studies and as one or several of the illustrated procedures may not apply or be available in particular contexts. Moreover, it should be noted that clinical or translational studies may not necessarily benefit from following these procedures if they apply well-validated protocols. However, the more of these methodical procedures that can be included in a given study, the more conclusive and mechanistically informed the resulting evidence.

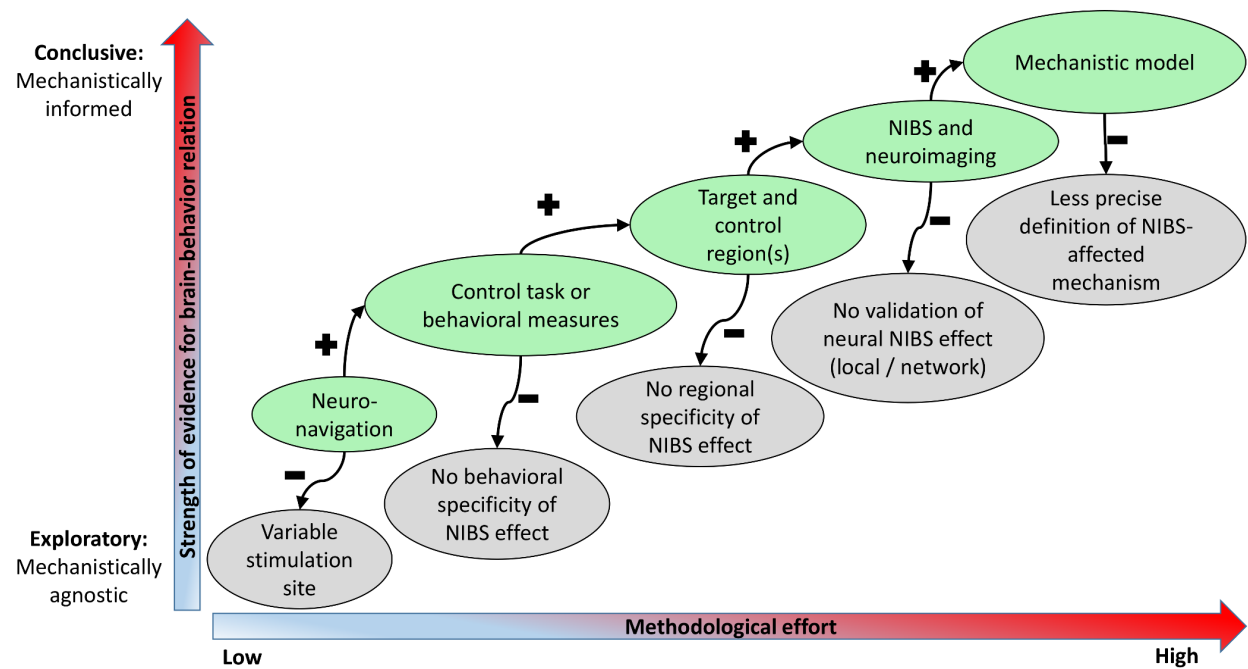


Figure 5. Examples of studies employing NIBS methods in a multi-methods approach to establish brain-behavior relations. **(a)** This study tested the hypothesis that working memory information is temporarily stored via “activity silent” synaptic mechanisms¹¹⁸. The authors first used fMRI to precisely localize cortical areas that represent category specific working memory contents (left panel). Afterwards, they used EEG in order to characterize the temporal dynamics of the hypothesized memory reactivation via single pulse TMS at the locations identified in the fMRI experiment (middle panel). They observed that a TMS pulse during the retention period, re-expressed latent working memories of unattended memory items (right panel). **(b)** This study tested the causal role of theta oscillations (~6 Hz) for working memory maintenance. The authors first identified for each individual the cortical generators of theta oscillations related to memory maintenance via MEG (left panel). Then the authors replicated their findings in a new experiment using EEG, which conveniently allows tracking of oscillatory neural entrainment via rhythmic TMS¹²⁰ (middle panel). Using this multi-method approach, the investigators demonstrated that by artificially entraining theta oscillations via TMS, it was possible to augment working memory performance (right panel). **(c)** This study investigated how the human brain represents beliefs about how our choices will influence those of others we interact with¹¹⁷. The authors first identified the region of interest using fMRI and computational modelling (left panel). The authors then used rTMS to inhibit the activity of the right temporoparietal junction (rTPJ), which was hypothesized to implement the social influence signal (middle panel). Additionally, the authors also used a remote control region (vertex) to test the regional specificity. After rTMS, participants performed the social task during fMRI and used computational modelling to study how mechanistic latent variables of behavior

where affected by the inhibitory rTMS protocol to the rTPJ compared to the control region (right panel). This multimethod approach, thus, allowed the authors to reveal a regional and functional specific causal role of the rTPJ in computing social influence signals.

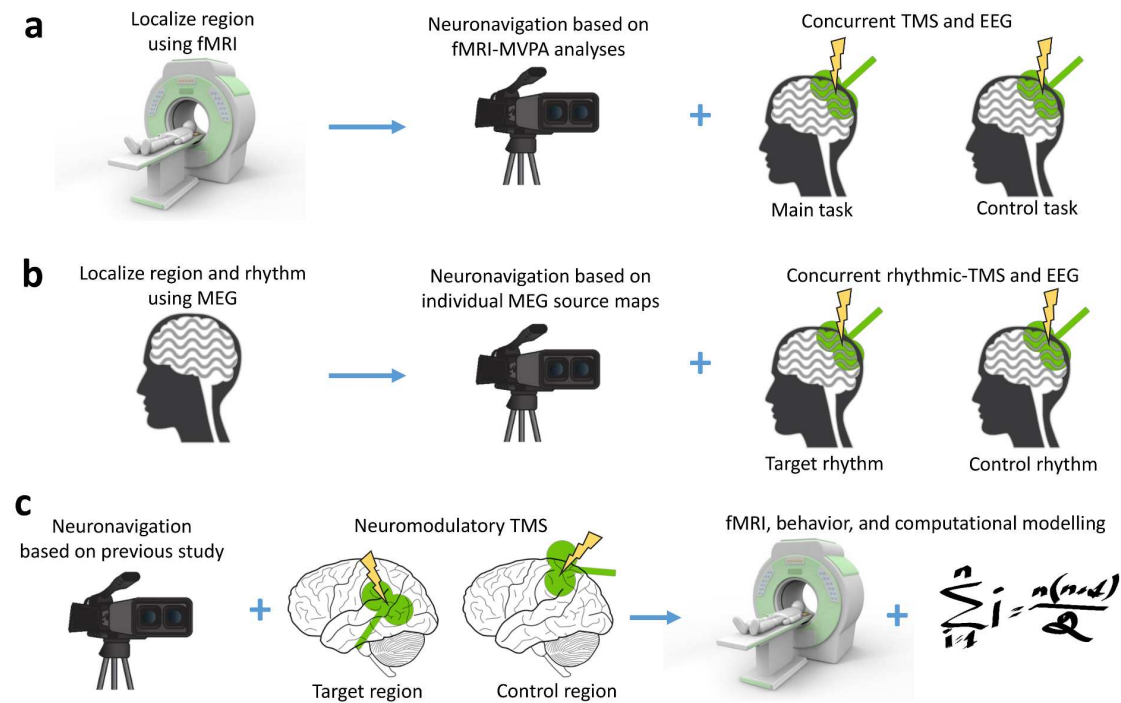
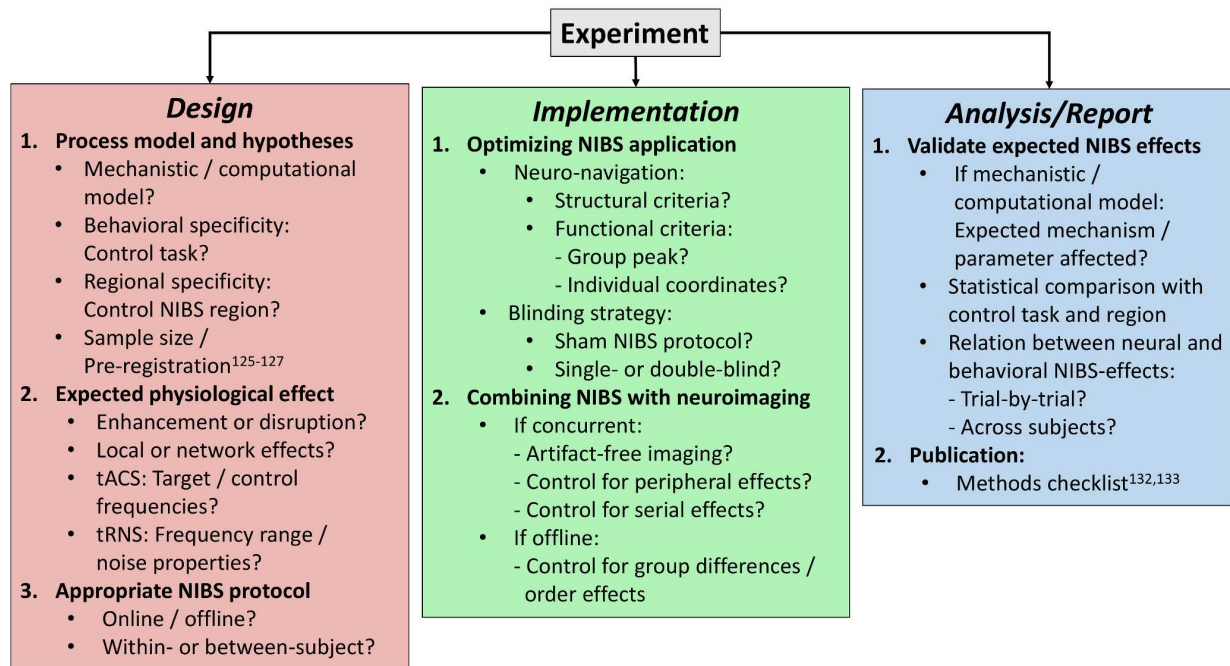


Figure 6. Multi-method approaches can be used to gain fundamental and more reliable insights on brain-behavior relations via NIBS. However, in order to carry out such studies involving high methodological effort (see Figure 4), it is crucial to have a clear work plan before conducting the study. This scheme shows an example of important aspects to consider in such a work plan before, during and after the execution of NIBS studies.



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BOX 1: Which aspects of neural processing are influenced by NIBS methods?

The results of research on basic neurophysiological NIBS effects have inspired many researchers to use NIBS techniques for investigating brain-behavior relationships. While the corresponding studies have led to a general consensus on the basic biophysical principles underlying each NIBS method, there is an ongoing debate about the precise neurophysiological processes that are stimulated by these techniques. Most studies on these issues have been conducted in primary motor cortex, so caution needs to be taken when extrapolating this knowledge to other cortical areas. For instance, it was originally suggested that TMS primarily excites the axons of superficial cortical interneurons, which then activate cortical output neurons¹³⁷. However, this notion may not apply to all cortical areas because which neurons are activated by an electrical current depends on the direction of the electrical field relative to the neuron, the sensitivity of a given type of neuron, the intensity of stimulation, the depth of penetration into excitable tissue, and other factors¹³⁸. The situation is further complicated by the fact that the gyrification of the human brain can vary between individuals and even within the same functionally defined area.

One strategy that has been proposed to address these issues is to estimate computational models of the most likely induced electric fields, which has led to the development of novel electrode configurations¹³⁹ that may help to predict NIBS-induced effects with greater accuracy^{106,111} (Box Figure 1a,b,c). For instance, modelling work suggests that conventional electrode montages might induce effects not only under the electrodes but also between them, and that for some montages the strongest fields may actually not lie under the electrodes (Box Figure 1a, top). While these efforts at modelling

tES-induced electric fields and effects on neurons may ultimately prove crucial for optimizing the efficiency of NIBS protocols, it is important to note that such models need to be physiologically validated^{9,36,106} and will need to be able to fully account for the well-established effects induced by more traditional protocols³⁶. For instance, neurophysiological work shows that both classic and novel electrode montages shown in Box Figure 1a reliably induce cortical excitability that depends on the stimulation polarity, with the conventional electrode montage inducing stronger effects immediately after stimulation but the novel ring electrode configuration effects being more prominent 30 minutes after the end of stimulation³⁶. Moreover, while the modelling sometimes suggests that the peak electric field in the classic montage may lie between rather than under the electrodes (e.g., see Box Figure 1a), the physiological data show that the induced effect is in fact maximal under the stimulating electrode³⁶. This puzzling discrepancy will need to be resolved and shows that while modelling will be useful to help optimizing NIBS protocols, physiological validation is crucial before jumping to conclusions about the spatial specificity and effectivity of any NIBS protocol^{140,141}.

Another promising route to deal with the relatively low degree of spatial focality offered by tDCS (Box Figure 1a) and TMS (Box Figure 1b) focusses on the development of new methods with improved spatial resolution. One such promising technology may be transcranial focused ultrasound stimulation (tFUS), which can induce cortical excitability changes with a resolution of millimeters as suggested by theoretical modelling and empirical work¹⁴² (Box Figure 1c). However, the neurophysiological underpinnings of these tFUS-induced changes of cortical excitability still need to be understood in much more detail before this method can be put to safe routine use.

In an attempt to answer the question “which aspects of neural processing are influenced by NIBS?”, researchers have tried to measure the neurophysiological influences of NIBS using a variety of methods including *in vitro*¹⁴¹, *in vivo*^{9,40,140} and *ex vivo* preparations¹⁴³. However, the results of these studies are rather variable. Therefore, it is crucial to investigate to what extent the results obtained from different approaches (e.g., *in vitro* and *ex vivo*) can be directly extrapolated to NIBS-induced effects in the healthy living human brain. In a recent study, researchers measured electric fields in the brain of non-human primates during tDCS/tACS both *in vivo* and *ex vivo*¹⁴⁴. They found significant differences in electrical field strength between *in vivo* and *ex vivo* measurements (Box Figure 1d), which may relate to biophysical changes of brain and head tissues that naturally accompany death. These results provide crucial evidence that accurate evaluation of the biophysical properties of NIBS techniques critically depend on *in vivo* measurements^{9,140,144} and that conclusions derived from *ex vivo* experiments need to be interpreted with care.

BOX 2: Definitions of NIBS-relevant terminology

Brain-derived neurotrophic factor (BDNF): A protein encoded by the *BDNF* gene that is highly relevant for NIBS research as it is known to be involved in various forms of synaptic plasticity including LTP/LTP (see below for a definition). Crucially, NIBS-induced neuroplasticity has been shown to depend on secretion of this protein in animal studies¹⁴⁵. In humans, brain-derived BDNF gene polymorphisms have been shown to have an impact on NIBS-induced plasticity¹⁴⁶. Thus, BDNF is one of the many factors that should

be taken into account when considering potential sources of behavioral and physiological variability in NIBS-induced effects (Figure 3).

Long-term potentiation (LTP): A facilitation of synaptic transmission that is considered to be one of the major mechanisms underlying learning and memory formation. The opposite phenomenon, **long-term depression (LTD)**, refers to inhibition of synaptic transmission. LTP and LTD are thought to be expressed at possibly every synapse in the mammalian brain¹⁴⁷. Long-lasting neurophysiological facilitation or inhibition induced by NIBS (depending on the method and protocol used and additional factors such as brain state and cognitive task) is believed to relate to LTP- or LTD-like changes.

Motor-evoked potentials (MEPs): Electrical potentials recorded from peripheral muscles in response to single-pulse electrical or magnetic stimulation of M1. MEP amplitudes are typically used to assess the level of cortico-spinal excitability induced by NIBS protocols. Excitatory or inhibitory NIBS protocols increase or decrease MEP amplitudes, respectively.

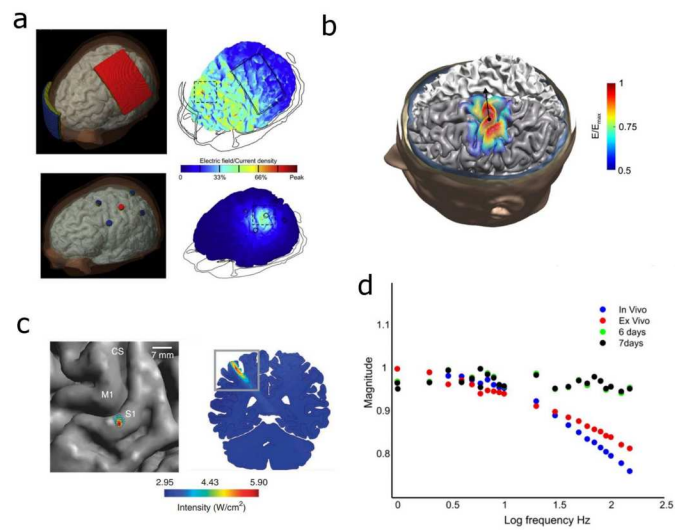
Phosphenes: Transient visual percepts resembling light flashes that can be induced by supra-threshold TMS pulses over V1²⁶ or by tACS in the ~8-35 Hz range, depending on the amount of light in the environment¹³⁰. For tACS in this frequency range (~8-35 Hz), such phosphenes need to be properly controlled for as they are difficult to differentiate from genuine neural entrainment. Moreover, whether the origin of tACS-induced phosphenes is cortical or retinal remains a matter of debate^{8,148}.

Stochastic Resonance (SR): A phenomenon referring to a situation where a signal that is too weak to be detected by a sensor is enhanced by adding an optimal level of noise. For instance, it has been shown that visual detection performance can be increased by

adding the right amount of noise to the visual stimulus; too much or too little noise results in poor detection performance or misperception of the visual stimulus. Recent studies have suggested that tRNS can be used as a tool to investigate the SR principle in the human cortex⁶³.

Box Figure 1. Spatial focality of NIBS methods estimated by electric field (EF) models.

(a) Conventional tDCS electrode montage for anodal stimulation of M1 with the cathodal electrode over the contralateral orbit (top left) and a more recent newly proposed 4x1 ring electrode configuration designed to improve the focality of the induced cortical EF (bottom left). The EF simulations based on a finite element model of the human head predict that the conventional electrode montage induces maximum EF mainly between the two electrodes, while the 4x1 ring electrode configuration induces more focalized effects over the target area¹³⁹. Adapted with permission from¹³⁹. **(b)** The predicted EF induced by a TMS coil positioned above left M1 with an orientation relative to central sulcus of 45°. The induced EF is relatively focal, but comparable to the EF induced by the tDCS 4x1 ring electrode configuration¹⁴⁹. Adapted with permission from¹⁴⁹. **(c)** The figure shows the acoustic intensity field (AIF) of the tFUS beam projected from above the primary somatosensory cortex. The AIF calculations suggest that tFUS should be much more focal than both TMS and tDCS as its effects are expressed in less than 1 cubic cm¹⁵⁰. Adapted with permission from¹⁵⁰. **(d)** Frequency response of intracranially measured voltages differ across different tACS frequencies between *in vivo* (blue) and *ex vivo* (red) states¹⁴⁴. Notably, any tACS frequency dependency is largely absent for the *ex vivo* measurements (green and black dots).



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